

**Inter-relationship of Friedman et al., OB-related  
U.S. Patent Applications and Issued U.S. Patents**

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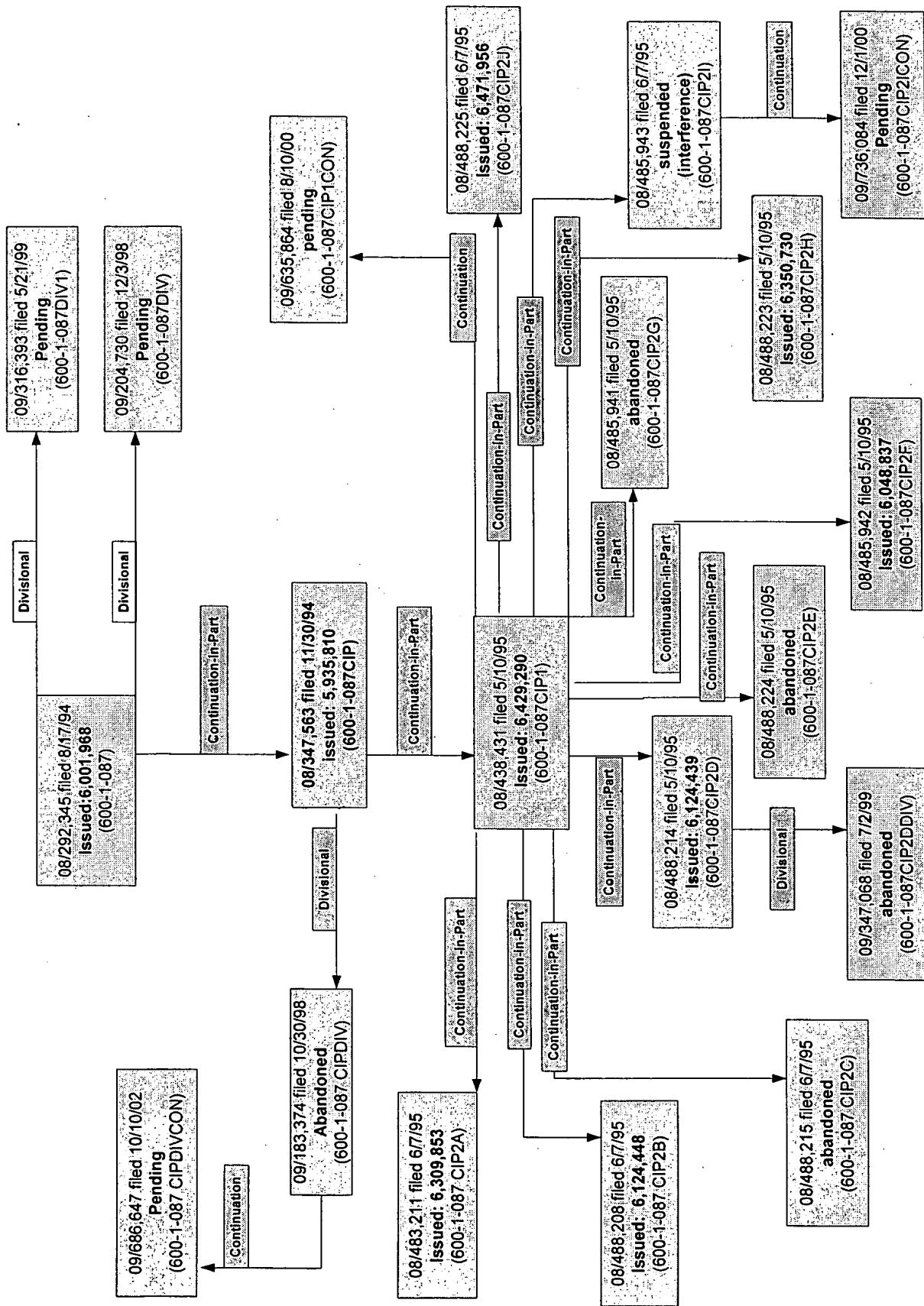
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**Tabulated Summary of Issued and Pending Claims**

<b>U.S. Patent Application/U.S. Patent No. and Status</b>	<b>Tab under which claims attached (if pending or issued)</b>	<b>Summary of Claimed subject matter</b>
6,001,968 (issued)	A	Isolated OB polypeptides; variants capable of modulating body weight; chemically synthesized polypeptides, recombinantly synthesized polypeptides and pharmaceutically acceptable compositions.
09/204,730 (pending)	B	OB fusion proteins.
09/316,393 (pending)	C	Methods for treating diabetes mellitus comprising administering OB polypeptide.
5,935,810 (issued)	D	Isolated polynucleotides encoding mammalian OB polypeptides; detectably labeled nucleic acids; cloning vectors; expression vectors; unicellular host cells transformed with the polynucleotides; mammalian cells containing OB polypeptide; recombinant methods of preparing OB polypeptide.
09/183,374 (abandoned)	-	Abandoned in favor of 09/686,647.
09/686,647 (pending)	E	Variants of OB polypeptide wherein specific amino acid residues are substituted with a non-conservative amino acid; dependent claims are directed to variants which are N-terminally modified; recombinantly produced, chemically synthesized; and pharmaceutical compositions comprising same.
6,429,290 (issued)	F	OB polypeptides capable of modulating body weight having one or more polymers attached thereto.

09/635,864 (pending)	G	Isolated nucleic acid molecules that encode an OB polypeptide.
6,309,853 (issued)	H	Isolated nucleic acids that encode analogs of an OB polypeptide.
6,124,448 (issued)	I	Isolated nucleic acid of at least 10 nucleotides that hybridize to specific nucleic acid sequences.
08/488,215 (abandoned)	-	-
6,124,439 (issued)	J	Antibodies to mammalian OB polypeptides; mammalian OB polypeptide variants; immortal cells lines that produce monoclonal antibodies; methods of preparing antibodies specific for mammalian OB polypeptides, and test kits comprising such antibodies.
09/347,068 (abandoned)		
08/448,224 (abandoned)		
6,048,837 (issued)	K	Method of modifying body weight of an animal comprising administering an OB polypeptide.
08/485,941 (abandoned)		
6,350,730 (issued)	L	Methods of modifying body weight of an animal comprising administering an OB polypeptide analog.
08/485,943 (suspended pending declaration of interference)	M	Methods of modifying the body weight of an animal comprising administering to the mammal a vector comprising a nucleic acid molecule that encodes an OB polypeptide.

09/736,084 (pending)	N	Methods of treating obesity in a mammal having a deficiency in functional leptin comprising administering intravenously to the mammal an adenoviral vector comprising a DNA sequence encoding a leptin operably linked to a promoter and expressing the DNA sequence, wherein the mammal exhibits a decrease in body weight, a decrease in serum glucose levels and/or a decrease in serum insulin levels.
6,471,956 (pending)	O	Immunogenic fragments of OB polypeptides; OB polypeptide analogs capable of modulating body weight wherein specific amino acid residues are substituted by another amino acid; and pharmaceutical compositions comprising the same.



# EXHIBIT A

6,001,968

53

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-continued

(A) DESCRIPTION: ob peptide

(v) FRAGMENT TYPE: Carboxyl terminal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Murine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Ser Arg Leu Gln Gln Gly Ser Leu Gln Asp Ile Leu Gln Gln Leu Asp Val  
1 5 10 15

Ser Pro Glu Cys  
20

15

What is claimed is:

1. An isolated mammalian OB polypeptide, said polypeptide having the sequence of a naturally occurring mammalian OB polypeptide, having as a mature protein about 145 amino acids, and capable of modulating body weight.
2. An isolated OB polypeptide capable of modulating body weight, the polypeptide comprising:
  - a) the amino acid sequence set out in SEQ ID NO: 2;
  - b) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 2;
  - c) the amino acid sequence set out in SEQ ID NO: 4; or
  - d) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 4.
3. An isolated OB polypeptide capable of modulating body weight, the polypeptide comprising:
  - a) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 2 having an N-terminal methionine or an N-terminal polyhistidine; or
  - b) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 4 having an N-terminal methionine or an N-terminal polyhistidine.
4. An isolated OB polypeptide capable of modulating body weight, the polypeptide comprising:
  - a) the amino acid sequence set out in SEQ ID NO: 5;
  - b) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 5;
  - c) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 5, having an N-terminal methionine or an N-terminal polyhistidine;
  - d) the amino acid sequence set out in SEQ ID NO: 6;
  - e) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 6; or
  - f) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 6 having an N-terminal methionine or an N-terminal polyhistidine.

5. A variant of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166 is substituted with a conserved amino acid.

20 6. A variant of an OB polypeptide, capable of modulating body weight comprising amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 121, 122, 126, 127, 128, 129, 139, 157, 159 and 163 is substituted with the particular amino acid present at the corresponding position in SEQ ID NO: 2.

25 7. A variant of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NO: 6 wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with a conserved amino acid.

30 8. A variant of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NO: 6 wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 120, 121, 125, 126, 127, 128, 138, 156, 158 and 162 is substituted with the particular amino acid present at the corresponding position in SEQ ID NO: 5.

35 9. An OB polypeptide according to claim 2 comprising amino acids 22-167 of SEQ ID NO. 4, optionally having an N-terminal methionine, in a pharmaceutically acceptable carrier.

40 10. A recombinant OB polypeptide according to any of claims 1-8.

11. A chemically synthesized OB polypeptide according to any of claims 1-8.

45 12. A pharmaceutical composition for reducing body weight of animal comprising the ob polypeptide of any of claims 1-8 and a pharmaceutically acceptable carrier.

\* \* \* \* \*

**Complete Listing of Pending Claims Pursuant to 37 C.F.R. §1.121**

In the following amendment, please cancel claims 10-14, 21-43 and 51 as drawn to non-elected subject matter, please also cancel claim 1 and claim 52. Please amend claims 57, 61, 66, 70 and 74 as indicated below to correct dependency on cancellation of claim 52. With the aforementioned amendments, the following listing of claims will replace all prior versions, and listings, of claims in the application:

Claims 1-52 (canceled).

53. (previously presented) An OB fusion protein comprising a non OB polypeptide joined via a peptide bond to an OB polypeptide capable of modulating body weight, the OB polypeptide having an amino acid sequence comprising:

- a) SEQ ID NO: 2;
- b) amino acids 22-167 of SEQ. ID. NO: 2;
- c) amino acids 22-167 of SEQ. ID. NO: 2 having an N terminal methionine;
- d) SEQ ID NO: 4;
- e) amino acids 22-167 of SEQ. ID. NO: 4;
- f) amino acids 22-167 of SEQ. ID. NO: 4, having an N-terminal methionine; or
- g) the fusion protein of any of (a) through (f) optionally having an N terminal methionine.

54. (previously presented) An OB fusion protein comprising a non OB polypeptide joined via a peptide bond to an OB polypeptide capable of modulating body weight; the OB polypeptide having an amino acid sequence comprising:

- a) SEQ ID NO: 5;
- b) amino acids 22-166 of SEQ ID NO: 5;
- c) amino acids 22-166 of SEQ ID NO: 5, having an N-terminal methionine;
- d) SEQ ID NO: 6;
- e) amino acids 22-166 of SEQ ID NO: 6;
- f) amino acids 22-166 of SEQ ID NO: 6, having an N-terminal methionine; or
- g) the fusion protein of any of (a) through (f) optionally having an N terminal methionine.

55. (previously presented) An OB fusion protein comprising a non OB polypeptide joined via a peptide bond to a variant of an OB polypeptide, said OB polypeptide variant capable of modulating body weight and comprising amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166 is substituted with:

- a) a conserved amino acid; or
- b) the amino acid present at the corresponding position in  
SEQ ID NO:2.

56. (previously presented) An OB fusion protein comprising a non OB polypeptide joined via a peptide bond to a variant of an OB polypeptide said OB polypeptide variant capable

of modulating body weight and comprising amino acids 22-166 of SEQ ID NO: 6 wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with:

- a) a conserved amino acid; or
- b) the amino acid present at the corresponding position in SEQ ID

NO:5. ~~an OB polypeptide or OB polypeptide variant fused to a non OB polypeptide or non OB polypeptide variant, wherein the fusion protein modulates body weight and comprises amino acids 22-166 of SEQ ID NO: 6, wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with:~~

57. (currently amended) The OB fusion protein of any one of claims 53 52 through 56, wherein said fusion protein comprises a protease specific cleavage site such that cleavage by the protease will release said OB polypeptide or OB polypeptide variant from said OB fusion protein.

58. (previously presented) The OB fusion protein of claim 57, wherein said protease specific cleavage site is between the non OB polypeptide and the OB polypeptide or OB polypeptide variant.

59. (previously presented) The OB fusion protein of claim 57, wherein said protease specific cleavage site is selected from the group consisting of a thrombin cleavage site and a Factor Xa cleavage site.

60. (previously presented) The OB fusion protein of claim 58, wherein said protease specific cleavage site is selected from the group consisting of a thrombin cleavage site and a Factor Xa cleavage site.

61. (currently amended) The OB fusion protein of any one of claims 53 52 through 56, wherein the non OB polypeptide is selected from the group consisting of a histidine tag and glutathione S transferase.

62. (previously presented) The OB fusion protein of claim 61, wherein said fusion protein comprises a protease specific cleavage site such that cleavage by the protease will release said OB polypeptide or OB polypeptide variant from said OB fusion protein.

63. (previously presented) The OB fusion protein of claim 62, wherein said protease specific cleavage site is between the non OB polypeptide and the OB polypeptide or OB polypeptide variant.

64. (previously presented) The OB fusion protein of claim 62, wherein said protease specific cleavage site is selected from the group consisting of a thrombin cleavage site and a Factor Xa cleavage site.

65. (previously presented) The OB fusion protein of claim 63, wherein said protease specific cleavage site is selected from the group consisting of a thrombin cleavage site and a Factor Xa cleavage site.

66. (currently amended) The OB fusion protein of any one of claims 53 52 through 56 wherein said non OB polypeptide is joined at the carboxy terminus of said OB polypeptide or said OB polypeptide variant.

67. (previously presented) The OB fusion protein of claim 66, wherein the non OB polypeptide is selected from the group consisting of a histidine tag and glutathione S transferase.

68. (previously presented) The OB fusion protein of claim 66, wherein said fusion protein comprises a protease specific cleavage site such that cleavage by the protease will release said OB polypeptide or OB polypeptide variant from said OB fusion protein.

69. (previously presented) The OB fusion protein of claim 68, wherein said protease specific cleavage site is between the non OB polypeptide and the OB polypeptide or OB polypeptide variant.

70. (currently amended) The OB fusion protein of any one of claims 53 52 through 56 wherein said non OB polypeptide is joined at the amino terminus of said OB polypeptide or said OB polypeptide variant.

71. (previously presented) The OB fusion protein of claim 70, wherein the non OB polypeptide is selected from the group consisting of a histidine tag and glutathione S transferase.

72. (previously presented) The OB fusion protein of claim 70, wherein said fusion protein comprises a protease specific cleavage site such that cleavage by the protease will release said OB polypeptide or OB polypeptide variant from said OB fusion protein.

73 (previously presented) The OB fusion protein of claim 72 wherein said protease specific cleavage site is between the non OB polypeptide and the OB polypeptide or OB polypeptide variant.

74. (currently amended) The OB fusion protein of any one of claims 53 52 through 56, wherein said non OB polypeptide facilitates the isolation of the OB fusion protein.

# EXHIBIT C

Attorney Docket No.: 600-1-087DIV1  
Serial No.: 09/316,393

## APPENDIX OF PENDING CLAIMS UPON ENTRY OF INSTANT AMENDMENT

52. (Amended) A method for treating or ameliorating diabetes mellitus which comprises administering to a patient afflicted with Type II diabetes a mammalian OB polypeptide, said polypeptide having the sequence of a naturally occurring mammalian OB polypeptide, having as a mature protein about 145 amino acids and capable of modulating body weight.

53. (Amended) A method for treating or ameliorating diabetes mellitus which comprises administering to a patient afflicted with Type II diabetes an OB polypeptide capable of modulating body weight, the polypeptide comprising:

- a) the amino acid sequence set out in SEQ ID NO: 2;
- b) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 2;
- c) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 2 having an N-terminal methionine or an N-terminal polyhistidine;
- d) the amino acid sequence set out in SEQ ID NO: 4;
- e) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 4; or
- f) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 4 having an N-terminal methionine or an N-terminal polyhistidine.

54. (Amended) A method for treating or ameliorating diabetes mellitus which comprises administering to a patient afflicted with Type II diabetes an OB polypeptide capable of modulating body weight, the polypeptide comprising:

- a) the amino acid sequence set out in SEQ ID NO: 5;
- b) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 5;
- c) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 5, having an N-terminal methionine or an N-terminal polyhistidine;
- d) the amino acid sequence set out in SEQ ID NO: 6;

- e) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 6; or
- f) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 6 having an N-terminal methionine or an N-terminal polyhistidine.

55. (Amended) A method for treating or ameliorating diabetes mellitus which comprises administering to a patient afflicted with Type II diabetes an OB polypeptide variant capable of modulating body weight, the variant comprising amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166 is substituted with a conserved amino acid.

56. (Amended) A method for treating or ameliorating diabetes mellitus which comprises administering to a patient afflicted with Type II diabetes an OB polypeptide variant capable of modulating body weight, the variant comprising amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 121, 122, 126, 127, 128, 129, 139, 157, 159 and 163 is substituted with the particular amino acid present at the corresponding position in SEQ ID NO: 2.

57. (Amended) A method for treating or ameliorating diabetes mellitus which comprises administering to a patient afflicted with Type II diabetes an OB polypeptide variant capable of modulating body weight, the variant comprising amino acids 22-166 of SEQ ID NO: 6 wherein one or more of amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 162 and 165 is substituted with a conserved amino acid.

58. (Amended) A method for treating or ameliorating diabetes mellitus which comprises administering to a patient afflicted with Type II diabetes an OB polypeptide variant capable of modulating body weight, the variant comprising amino acids 22-166 of SEQ ID

NO: 6 wherein one or more of amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 120, 121, 125, 126, 127, 128, 138, 156, 158 and 162 is substituted with the particular amino acid present at the corresponding position in SEQ ID

NO: 5.

59. A method for treating or ameliorating diabetes mellitus, in a patient in need thereof, which comprises administering to an obese type II diabetic an effective amount of an OB polypeptide, an OB polypeptide variant, an OB polypeptide analog, or a pharmaceutically acceptable salt thereof.

61. A method for treating or ameliorating diabetes mellitus, in a patient in need thereof, which comprises administering to an obese type II diabetic an effective amount of leptin, a leptin mimetic, or a pharmaceutically acceptable salt thereof.

# EXHIBIT D

5,935,810

77

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-continued

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 40 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (primer)

- (A) DESCRIPTION: PCR 5 primer for amplifying murine ob cDNA sequence

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GTATCTCTCG AGAAAAGAGT GCCTATCCAG AAAGTCCAGG

40

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 31 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (primer)

- (A) DESCRIPTION: PCR 3 primer for amplifying murine ob cDNA sequence

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GCGCGAATTTC TCAGGATTCA GGGCTAACAT C

31

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: linear
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

- (A) DESCRIPTION: tetrapeptide at N-terminus of renatured murine

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Murine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Gly Ser His Met

What is claimed is:

1. An isolated polynucleotide encoding a mammalian OB polypeptide, said polypeptide capable of modulating body weight.

2. An isolated polynucleotide encoding an OB polypeptide capable of modulating body weight, the polypeptide comprising:

- a) the amino acid sequence set out in SEQ ID NO: 2;
- b) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 2;
- c) the amino acid sequence set out in SEQ ID NO: 4; or
- d) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 4.

3. An isolated polynucleotide encoding an OB polypeptide capable of modulating body weight, the polypeptide comprising:

- a) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 2 having an N-terminal methionine or an N-terminal polyhistidine; or

- b) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 4 having an N-terminal methionine or an N-terminal polyhistidine.

4. An isolated polynucleotide encoding an OB polypeptide capable of modulating body weight, the polypeptide comprising:

- a) SEQ ID NO: 5;
- b) amino acids 22-166 of SEQ ID NO: 5;

- c) amino acids 22-166 of SEQ ID NO: 5, having an N-terminal methionine or an N-terminal polyhistidine; d) SEQ ID NO: 6;
- c) amino acids 22-166 of SEQ ID NO: 6; or
- f) amino acids 22-166 of SEQ ID NO: 6 having an N-terminal methionine or an N-terminal polyhistidine.

5. An isolated polynucleotide encoding an OB polypeptide capable of modulating body weight in a mammal, the polynucleotide being selected from the group consisting of:

- 10 a) a polynucleotide encoding the amino acid sequence set out in SEQ ID NO: 2;
- b) a polynucleotide encoding the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 2;
- c) a polynucleotide encoding the amino acid sequence set out in SEQ ID NO: 4;
- d) a polynucleotide encoding the amino acid sequence set out in amino acids 22-167 of SEQ ID NO 4; and
- e) a polynucleotide which hybridizes under moderate stringency hybridization conditions to the polynucleotide of any one of a) through d).

6. The isolated polynucleotide of claim 5 subpart e) wherein said moderate stringency hybridization conditions are 40% formamide with 5x or 6x SSC.

7. An isolated polynucleotide comprising the DNA sequence set out as SEQ ID NO:22.

8. An isolated polynucleotide encoding an OB polypeptide capable of modulating body weight having 83% or more amino acid identity with an OB polypeptide comprising an amino acid sequence set out in SEQ ID NOS: 2, 4, 5, 6, 23 or 25.

9. An isolated mammalian genomic polynucleotide encoding an OB polypeptide capable of modulating body weight, the polypeptide comprising the amino acid sequence set out in SEQ ID NOS: 2, 4, 5, 6, 23 or 25.

10. An isolated polynucleotide encoding a conserved variant of an OB polypeptide, capable of nodulating body weight, comprising amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166 is substituted with:

- a) the amino acid present in SEQ ID NO: 3 at the corresponding position; or
- b) a conserved amino acid.

11. An isolated polynucleotide encoding a conserved variant of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NO: 6 wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with:

- a) the amino acid present in SEQ ID NO: 5 at the corresponding position; or
- b) a conserved amino acid.

12. A detectably labeled nucleic acid of at least 10 nucleotides hybridizable under moderate stringency hybridization conditions to a polynucleotide according to any one of claims 1 to 4 or 7.

13. A cloning vector which comprises a polynucleotide according to any one of claims 1 to 11.

14. An expression vector which comprises a polynucleotide according to any one of claims 1 to 11.

15. An expression vector which comprises a polynucleotide according to any one of claims 1 to 11 operatively associated with an expression control sequence.

16. The expression vector of claim 15 wherein said expression control sequence is selected from the group consisting of the immediate early promoters of hCMV, early promoters of SV40, early promoters of adenovirus, early promoters of vaccinia, early promoters of polyoma, late promoters of SV40, late promoters of adenovirus, late promoters of vaccinia, late promoters of polyoma, the lac system, the trp system, the TAC system, the T'AC system, the major operator and promoter regions of phage  $\lambda$  control regions of fd coat protein, 3-phosphoglycerate kinase promoter, acid phosphatase promoter, and promoters of yeast  $\alpha$  mating factor.

17. A unicellular host transformed with a polynucleotide according to any one of claims 1 to 11.

18. The unicellular host according to claim 17 wherein the host cell is selected from the group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*, yeast, CHO, R1.1, B-W, L-M, COS1, COS7, BSC1, BSC40, BMT10, and SF9 cells.

19. The unicellular host according to claim 17 wherein the unicellular host is a yeast host selected from the group consisting of *Saccharomyces*, *Pichia*, *Candida*, *Hansenula*, and *Torulopsis*.

20. A mammalian cell containing a chromosomal OB polypeptide encoding DNA sequence and modified in vitro to permit higher expression of OB polypeptide by means of a homologous recombinational event consisting of inserting an expression regulatory sequence in functional proximity to the chromosomal OB polypeptide encoding sequence.

21. A cell according to claim 20 wherein the expression regulatory sequence is an OB polypeptide expression regulatory sequence and the homologous recombinational event replaces a mutant chromosomal OB polypeptide expression regulatory sequence.

22. A cell according to claim 20 wherein the expression regulatory sequence insert is not an OB polypeptide regulatory sequence.

23. A mammalian cell containing a vector comprising OB polypeptide encoding DNA sequence and modified in vitro to permit higher expression of OB polypeptide by means of a homologous recombinational event consisting of inserting an expression regulatory sequence in functional proximity to the vector OB polypeptide encoding sequence.

24. A cell according to claim 23 wherein the expression regulatory sequence is an OB polypeptide expression regulatory sequence and the homologous recombinational event replaces a mutant vector OB polypeptide expression regulatory sequence.

25. A cell according to claim 23 wherein the expression regulatory sequence insert is not an OB polypeptide regulatory sequence.

26. A method for preparing an OB polypeptide, the method comprising:

- a) culturing a host according to claim 17 under conditions that provide for expression of the OB polypeptide; and
- b) recovering the expressed OB polypeptide.

27. A method for preparing an OB polypeptide, the method comprising:

- a) culturing a host which has been transfomed or transfected with a polynucleotide encoding a polypeptide capable of modulating body weight having 83% or more amino acid identity with an OB polypeptide comprising an amino acid sequence set out in SEQ ID NOS: 2, 4, 5, 6, 23 or 25; and
- b) recovering the expressed OB polypeptide.

\* \* \* \* \*

# EXHIBIT E

## COMPLETE LISTING OF PENDING CLAIMS PURSUANT TO 37 C.F.R. §1.121

This listing of claims will replace all prior versions, and listings, of claims in the application:

Claims 1-58 [canceled]

59. [previously presented] A variant of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NO: 2 or 4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166, according to the numbering of SEQ ID NO: 4, is substituted with a non-conservative amino acid.

60. [previously presented] A variant of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NO: 5 or 6 wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165, according to the numbering of SEQ ID NO: 6, is substituted with a non-conservative amino acid.

61. [previously presented] The OB polypeptide of claim 59 having an N-terminal methionine or an N-terminal polyaminoacid.

62. [previously presented] The OB polypeptide of claim 60 having an N-terminal methionine or an N-terminal polyaminoacid.

63. [previously presented] A recombinant OB polypeptide according to any of claims 59-62.

64. [previously presented] A chemically synthesized OB polypeptide according to any of claims 59-62.

65. [previously presented] A pharmaceutical composition comprising the OB polypeptide of any of claims 59-62 and a pharmaceutically acceptable carrier.--

-continued

(B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(iii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: N-terminal His-tag

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro  
 1 5 10 15

Arg Gly Ser Pro  
 20

What is claimed is:

1. An OB polypeptide, capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutically acceptable carrier, wherein said OB polypeptide is a mammalian OB polypeptide having the sequence of a naturally occurring mammalian OB polypeptide and having as a mature protein about 145 amino acids.

2. An OB polypeptide, capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutically acceptable carrier, said OB polypeptide comprising the amino acid sequence set out in:

- a) SEQ ID NO:2;
- b) amino acids 22-167 of SEQ ID NO: 2;
- c) SEQ ID NO:4; or
- d) amino acids 22-167 of SEQ ID NO: 4.

3. An OB polypeptide, capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutically acceptable carrier, said OB polypeptide comprising the amino acid sequence set out in:

- a) SEQ ID NO: 5;
- b) amino acids 22-166 of SEQ ID NO. 5;
- c) SEQ ID NO. 6; or
- d) amino acids 22-166 of SEQ ID NO. 6.

4. An OB polypeptide, capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutically acceptable carrier, wherein said OB polypeptide has 83 percent or greater amino acid sequence identity to the OB polypeptide amino acid sequence set out in SEQ ID NOS: 2, 4, 5 or 6.

5. An OB polypeptide, capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutically acceptable carrier, wherein said OB polypeptide is a variant wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166, according to the numbering of SEQ ID NO: 4, is substituted with a conserved amino acid.

6. An OB polypeptide, capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutically acceptable carrier, wherein said OB polypeptide is a variant wherein one or more of amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 121, 122, 126, 127, 128, 129, 139, 157, 159 and 163, according to the numbering of SEQ ID NO: 4, is substituted with the particular amino acid present at the corresponding position in SEQ ID NO: 2.

7. An OB polypeptide, capable of modulating body weight, having one or more polymers attached thereto,

optionally in a pharmaceutically acceptable carrier, wherein said OB polypeptide is a variant wherein one or more of amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165, according to the numbering of SEQ ID NO: 6, is substituted with a conserved amino acid.

8. An OB polypeptide, capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutically acceptable carrier, wherein said OB polypeptide is a variant wherein one or more of amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 120, 121, 125, 126, 127, 128, 138, 156, 158 and 162, according to the numbering of SEQ ID NO: 6, is substituted with the particular amino acid at the corresponding position in SEQ ID NO: 5.

9. The OB polypeptide of any of claims 1-8, wherein at least one of said polymers is a water soluble polymer.

10. The OB polypeptide of claim 9, wherein said water soluble polymer is selected from the group consisting of carboxymethylcellulose and dextran.

11. The OB polypeptide of claim 9, wherein said water soluble polymer is selected from the group consisting of copolymers of ethylene glycol/propylene glycol, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1, 3,6-trioxane, ethylene/maleic anhydride copolymer, homopolymers of polyaminoacids, random copolymers of polyaminoacids, poly(n-vinyl pyrrolidone)polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol.

12. The OB polypeptide of claim 9, wherein said water-soluble polymer is polyethylene glycol.

13. The OB polypeptide of claim 12 which is mono-, di-, tri- or tetrapegylated.

14. The OB polypeptide of claim 13 which is N-terminal monopegylated.

15. The OB polypeptide of any of claims 1-8, wherein at least one of said polymers is a pharmaceutically acceptable polymer.

16. The OB polypeptide of claim 15, wherein said pharmaceutically acceptable polymer is a water soluble polymer.

17. The OB polypeptide of any of claims 1-8, wherein at least one of said polymers is a polyamino acid.

18. The OB polypeptide of any of claims 1-8, wherein at least one of said polymers is a branched or unbranched polymer.

19. The OB polypeptide of any of claims 1-8, wherein at least one of said polymers is N-terminally attached to said polypeptide.

20. The OB polypeptide of any of claims 1-8, wherein at least one of said polymers is C-terminally attached to said polypeptide.

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21. The OB polypeptide of any of claims 1-8, wherein at least one of said polymers is attached by at least one covalent bond through an amino acid residue of said polypeptide via a reactive group.

22. The OB polypeptide of claim 21, wherein said reactive group is a free amino or carboxyl group.

23. The OB polypeptide of claim 21, wherein said amino acid residue is selected from the group consisting of lysine, aspartic acid and glutamic acid.

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24. The OB polypeptide of any of claims 1-8, wherein the number of said polymers attached is one, two, three or four.

25. The OB polypeptide of claim 24 wherein said two, three or four polymers are the same polymer.

26. The OB polypeptide of claim 24 wherein said two, three or four polymers are two, three or four different polymers.

\* \* \* \* \*

# EXHIBIT G

The Examiner set forth an eleven-way restriction requirement. Applicants herewith elect the claims of **Group I** directed to polynucleotides, host cells and recombinant methods of protein production, *i.e.*, claims 1-14, and 23-27. This election is made without traverse. Applicants withdraw claims 15-22 and 28-58 from consideration, without prejudice or disclaimer, as being directed to non-elected subject matter. Applicants reserve the right to prosecute these withdrawn claims in further divisional applications at a later date.

## II. Amendment

After election of Group I claims, Applicants request that claims 1-14 and 23-27 be canceled and the following new set of claims be inserted therefor:

59. (NEW) An isolated nucleic acid molecule selected from the group consisting of:

- a) a nucleic acid having the sequence of SEQ ID NO:1;
- b) a nucleic acid molecule having the sequence of SEQ ID NO:3;
- c) a nucleic acid molecule having the sequence of SEQ ID NO:22; and
- d) a nucleic acid sequence that hybridizes to any one of the nucleic acids of (a), (b), and (c) and
- e) a nucleic acid sequence that encodes an expression product of an amino acid sequence encoded by any of the foregoing nucleic acid sequences.

60. (NEW) An isolated nucleic acid molecule that encodes an OB polypeptide capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutical carrier, wherein said OB polypeptide encoded by said isolated nucleic acid is a mammalian OB polypeptide having the sequence of a naturally occurring mammalian OB polypeptide and having as a mature protein about 145 amino acids.

61. (NEW) An isolated nucleic acid molecule that encodes an OB polypeptide capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutical carrier, wherein said OB polypeptide encoded by said isolated nucleic acid comprises the amino acid sequence set out in:

- a) SEQ ID NO:2;
- b) amino acids 22-167 of SEQ ID NO:2;
- c) SEQ ID NO:4 or
- d) amino acids 22-167 of SEQ ID NO:4.

62. (NEW) An isolated nucleic acid molecule that encodes an OB polypeptide capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutical carrier, wherein said OB polypeptide encoded by said isolated nucleic acid comprises the amino acid sequence set out in

- a) SEQ ID NO:5;
- b) amino acids 22-166 of SEQ ID NO:5;
- c) SEQ ID NO:6 or
- d) amino acids 22-166 of SEQ ID NO:6.

63. (NEW) An isolated nucleic acid molecule that encodes an OB polypeptide capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutical carrier, wherein said OB polypeptide encoded by said isolated nucleic acid has 83 percent or greater amino acid sequence identity to the OB polypeptide amino acid sequence set out in SEQ ID NO:2, 4, 5 or 6.

64. (NEW) An isolated nucleic acid molecule that encodes an OB polypeptide, capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutically acceptable carrier, wherein said OB polypeptide encoded by said isolated nucleic acid is an OB polypeptide variant in which one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166, according to the numbering of SEQ ID NO: 4, is substituted with a conserved amino acid.

65. (NEW) An isolated nucleic acid molecule that encodes an isolated nucleic acid molecule that encodes an OB polypeptide, capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutically acceptable carrier, wherein said OB polypeptide encoded by said isolated nucleic acid is an OB polypeptide variant in which one or more of amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 121, 122, 127, 128, 129, 139, 157, 159 and 163, according to the numbering of SEQ ID NO: 4, is substituted with the particular amino acid present at the corresponding position in SEQ ID NO: 2.

66. (NEW) An isolated nucleic acid molecule that encodes an OB polypeptide, capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutically acceptable carrier, wherein said OB polypeptide encoded by said isolated nucleic acid is an OB polypeptide variant in which one or more of amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127,

128, 131, 138, 156, 158, 162 and 165, according to the numbering of SEQ ID NO: 6, is substituted with a conserved amino acid.

67. (NEW) An isolated nucleic acid molecule that encodes an OB polypeptide, capable of modulating body weight, having one or more polymers attached thereto, optionally in a pharmaceutically acceptable carrier, wherein said OB polypeptide encoded by said isolated nucleic acid is an OB polypeptide variant in which one or more of amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 120, 121, 125, 126, 127, 128, 138, 156, 158 and 162, according to the numbering of SEQ ID NO: 6, is substituted with the particular amino acid at the corresponding position in SEQ ID NO: 5.

68. (NEW) The nucleic acid of any of claims 59 to 67, wherein at least one of said polymers is a polyamino acid.

69. (NEW) The nucleic acid of claim 68, wherein said polyamino acid is N-terminally attached to said polypeptide.

70. (NEW) The nucleic acid of claim 68, wherein said polyamino acid is C-terminally attached to said polypeptide.

71. (NEW) The nucleic acid of any one of claim 59 to 70, wherein said nucleic acid is selected from the group consisting of DNA or RNA.

72. (NEW) The nucleic acid of any one of claims 59 to 70, wherein said nucleic acid is detectably labeled.

73. (NEW) A cloning vector comprising a nucleic acid of any one of claims 59 to 70.

74. (NEW) An expression construct comprising a nucleic acid molecule of any one of claims 59 to 70 operatively associated with an expression control sequence.

75. (NEW) The expression vector of claim 74, wherein said expression control sequence is selected from the group consisting of cytomegalovirus hCMV immediate early gene, the early or late promoters of SV40 or adenovirus, the lac system, the trp system, the TAC system, the major operator and promoter regions of phage  $\lambda$ , the control regions of fd coat protein, the promoter for 3-phosphoglycerate kinase, the promoters of acid phosphatase, and the promoters of the yeast  $\alpha$ -mating factors.

76. (NEW) A unicellular host transfected with a cloning vector of claim 73.

77. (NEW) A host cell transformed with an expression construct of claim 74.

78. (NEW) The host cell of claim 77, wherein said host cell is selected from the group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*, Pichia yeasts, CHO, R1.1, B-W, L-M, COS-1, COS-7, BSC1, BSC40, BMT10 and cells, plant cells, insect cells and human cells in tissue culture.

79. (NEW) A method for preparing an OB polypeptide comprising:

- culturing a host cell of claim 76 or 77 under conditions that allow the expression of said OB polypeptide; and
- recovering the expressed OB polypeptide.

80. (NEW) The method of claim 79, wherein said host cell is a bacterial cell.

81. (NEW) The method of claim 79, wherein the host cell is a yeast cell.

82. (NEW) The method of claim 79, further comprising:

- chromatographing the polypeptide on a Ni-chelation column; and
- purifying the polypeptide by gel filtration.

83. (NEW) The method of claim 82, further comprising after step (c) and prior to step (d), chromatographing the OB polypeptide on a strong cation exchanger column.

### III. Additional Remarks

Applicants have canceled claims 1-14 and 23-27, without prejudice or disclaimer and inserted therefore new claims 59-83. Applicants request examination of these new claims. The new claims are fully supported by the specification as filed and entry of these new claims does not constitute an introduction of new matter into the instant application.

New claims 59-70 are directed to nucleic acids and correspond to the polypeptide claims that have been indicated as allowed in the parent application U.S. Serial No. 08/438,431, in which the issue fee was paid August 20, 2000. The new claims 59-70 in the present case correspond to the allowed claims from U.S. Serial No. 08/438,431 as follows:

Claims indicated as allowed in 08/438,431	Corresponding new claim presented herein
81	60

-continued

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

Met	Gly	Ser	Ser	His	His	His	His	His	Ser	Ser	Gly	Leu	Val	Pro
1				5				10				15		
Arg	Gly	Ser	His	Met										20

What is claimed is:

1. An isolated nucleic acid encoding an analog of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NOS: 2 or 4, wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163, and 166 is substituted with another amino acid.

2. An isolated nucleic acid encoding an analog of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NO: 4 wherein the analog is selected from the group consisting of polypeptides wherein:

- (a) the serine residue at position 53 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine;
- (b) the serine residue at position 98 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine; and
- (c) the arginine residue at position number 92 is substituted with asparagine, lysine, histidine, glutamine, glutamic acid, aspartic acid, serine, threonine, methionine, or cysteine.

3. An isolated nucleic acid encoding an analog of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NOS: 2 or 4, wherein the analog is selected from the group consisting of polypeptides wherein:

- (a) one or more aspartic acid residues is substituted with glutamic acid;
- (b) one or more isoleucine residues is substituted with leucine;
- (c) one or more glycine or valine residues is substituted with alanine;
- (d) one or more arginine residues is substituted with histidine;
- (e) one or more tyrosine or phenylalanine residues is substituted with tryptophan;
- (f) one or more of residues 121 through 128 is substituted with glycine or alanine; and
- (g) one or more residues at positions 54 through 60 or 118 through 166 is substituted with lysine, glutamic acid, cysteine, or proline.

4. An isolated nucleic acid encoding an OB polypeptide comprising amino acids 22-167 of SEQ ID Nos. 2 or 4 or amino acids 22-166 of SEQ ID Nos. 5 or 6 and capable of modulating body weight said OB polypeptide having an N-terminal amino acid sequence selected from the group consisting of:

- (a) SEQ ID NO: 38;
- (b) SEQ ID NO: 98;

- 15 (c) SEQ ID NO: 26;
- (d) SEQ ID NO: 27;
- (e) SEQ ID NO: 28;
- (f) SEQ ID NO: 99; and
- (g) a glycine-serine-proline sequence.
- 20 5. An isolated nucleic acid encoding an analog of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NOS: 2 or 4, wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163, and 166 is substituted with another amino acid and wherein said analog has an N-terminal amino acid sequence selected from the group consisting of:
- (a) SEQ ID NO: 38;
- (b) SEQ ID NO: 98;
- (c) SEQ ID NO: 26;
- (d) SEQ ID NO: 27;
- (e) SEQ ID NO: 28;
- (f) SEQ ID NO: 99; and
- (g) a glycine-serine-proline sequence.
- 25 6. An isolated nucleic acid encoding an analog of an OB polypeptide comprising an amino acid sequence of SEQ ID NOS: 2 or 4, wherein the analog is a truncated analog selected from the group consisting of polypeptides wherein:
- (a) one or more residues at positions 121 to 128 are deleted;
- (b) residues 1-116 are deleted;
- (c) residues 1-21 and 54 to 167 are deleted;
- (d) residues 1-60 and 117 to 167 are deleted;
- (e) residues 1-60 are deleted;
- (f) residues 1-53 are deleted;
- (g) an analog of subpart (a) wherein residues 1-21 are deleted; and
- (h) an analog of subpart (a) through (g) having an N-terminal amino acid or amino acid sequence selected from the group consisting of:
- (1) methionine,
- (2) SEQ ID NO: 38,
- (3) SEQ ID NO: 98,
- (4) SEQ ID NO: 26,
- (5) SEQ ID NO: 27,
- (6) SEQ ID NO: 28,
- (7) SEQ ID NO: 99; and
- (8) a glycine-serine-proline sequence.
- 30 7. An isolated nucleic acid encoding an analog of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NOS: 5 or 6, wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120,

121, 125, 126, 127, 128, 131, 138, 156, 158, 162, and 165 is substituted with another amino acid.

8. An isolated nucleic acid encoding an analog of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NO: 6 wherein the analog is selected from the group consisting of polypeptides wherein:

- (a) the serine residue at position 52 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine;
- (b) the serine residue at position 97 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine; and
- (c) the arginine residue at position number 91 is substituted with asparagine, lysine, histidine, glutamine, glutamic acid, aspartic acid, serine, threonine, methionine, or cysteine.

9. An isolated nucleic acid encoding an analog of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NOS: 5 or 6, wherein the analog is selected from the group consisting of polypeptides wherein:

- (a) one or more aspartic acid residues is substituted with glutamic acid;
- (b) one or more isoleucine residues is substituted with leucine;
- (c) one or more glycine or valine residues is substituted with alanine;
- (d) one or more arginine residues is substituted with histidine;
- (e) one or more tyrosine or phenylalanine residues is substituted with tryptophan;
- (f) one or more of residues 120 through 127 is substituted with glycine or alanine; and
- (g) one or more residues at positions 53 through 59 or 117 through 165 is substituted with lysine, glutamic acid, cysteine, or proline.

10. An isolated nucleic acid encoding an analog of an OB polypeptide comprising an amino acid sequence of SEQ ID NOS: 5 or 6, wherein the analog is a truncated analog selected from the group consisting of polypeptides wherein:

- (a) one or more residues at positions 120 to 127 are deleted;
- (b) residues 1-115 are deleted;
- (c) residues 1-21 and 53 to 166 are deleted;
- (d) residues 1-59 and 116 to 166 are deleted;
- (e) residues 1-59 are deleted;
- (f) residues 1-52 are deleted;
- (g) an analog of subpart (a) wherein residues 1-21 are deleted; and
- (h) an analog of subpart (a) through (g) having an N-terminal amino acid or amino acid sequence selected from the group consisting of:

- (1) methionine,
- (2) SEQ ID NO: 38,

(3) SEQ ID NO: 98,  
(4) SEQ ID NO: 26,  
(5) SEQ ID NO: 27,  
(6) SEQ ID NO: 28,  
(7) SEQ ID NO: 99, and  
(8) a glycine-serine-proline sequence.

11. An isolated nucleic acid encoding an analog of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NOS: 5 or 6, wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162, and 165 is substituted with another amino acid and wherein said analog has an N-terminal amino acid sequence selected from the group consisting of:

- (a) SEQ ID NO: 38;
- (b) SEQ ID NO: 98;
- (c) SEQ ID NO: 26;
- (d) SEQ ID NO: 27;
- (e) SEQ ID NO: 28;
- (f) SEQ ID NO: 99; and
- (g) a glycine-serine-proline sequence.

12. The isolated nucleic acid according to claim 1, 2, 3, 4-6 or 7 which is a DNA molecule.

13. A detectably labeled nucleic acid molecule of at least 10 nucleotides hybridizable under moderate stringency hybridization conditions to a DNA molecule according to claim 12.

14. A vector which comprises a DNA molecule according to claim 12.

15. An expression vector which comprises a DNA molecule according to claim 12 operatively associated with an expression control sequence.

16. An unicellular host transformed or transfected with an expression vector of claim 15.

17. A unicellular host according to claim 16, wherein the unicellular host is selected from the group consisting of bacteria, yeast, mammalian cells, plant cells, insect cells, and human cells in tissue culture.

18. The unicellular host of claim 16, wherein the unicellular host is selected from the group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*, yeast, CHO, R1.1, B-W, LM, COS 1, COS 7, BSC1, BSC40, BMT10, and SF9 cells.

19. A unicellular host according to claim 16 wherein the unicellular host is a yeast host selected from the group consisting of *Saccharomyces*, *Pichia*, *Candida*, *Hansenula* and *Itorulopsis*.

20. A method for preparing an OB polypeptide comprising:

- (a) culturing a cell according to claim 16 under conditions that provide for expression of the OB polypeptide; and
- (b) recovering the expressed OB polypeptide.

21. The method according to claim 20 wherein the cell is a bacterium or a yeast.

\* \* \* \* \*

# Exhibit I

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169

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-continued

Ile	Leu	Thr	Ser	Met	Pro	Ser	Arg	Asn	Val	Leu	Gln	Ile	Ser	Asn	Asp
65										75					80
Leu	Glu	Asn	Leu	Arg	Asp	Leu	Leu	His	Val	Leu	Ala	Phe	Ser	Lys	Ser
	85							90					95		
Cys	His	Leu	Pro	Trp	Ala	Ser	Gly	Leu	Glu	Thr	Leu	Asp	Ser	Leu	Gly
	100							105					110		
Gly	Val	Leu	Glu	Ala	Ser	Gly	Tyr	Ser	Thr	Glu	Val	Val	Ala	Leu	Ser
	115						120				125				
Arg	Leu	Gln	Gly	Ser	Leu	Gln	Asp	Met	Leu	Trp	Gln	Leu	Asp	Leu	Ser
	130						135				140				
Pro	Gly	Cys													
	145														

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

Met	Gly	Ser	Ser	His	His	His	His	His	Ser	Ser	Gly	Leu	Val	Pro
1				5				10				15		
Arg	Gly	Ser	His	Met										
	20													

What is claimed is:

1. An isolated nucleic acid of at least 10 nucleotides hybridizable under moderate stringency conditions to a non-coding region of an OB nucleic acid, which non-coding region is selected from the group consisting of an intron, a 5' non-coding region, and a 3' non-coding region of SEQ ID NOS: 1, 3, 22 or 24.
2. An oligonucleotide primer of at least 10 nucleotides for amplifying mouse or human genomic DNA encoding an OB polypeptide, said primer hybridizable under moderate stringency conditions to any of SEQ ID NOS: 1, 3, 22 or 24.
3. An oligonucleotide according to claim 2 which is selected from the group consisting of:  
HOB 1gR 5'-GACTATCTGGGTCCAGTGCC-3' (SEQ ID NO. 29);

<sup>35</sup> HOB 1gR 5'-GACTATCTGGGTCCAGTGCC-3' (SEQ ID NO. 30);

HOB 2gF 5'-CCACATGCTGAGCACTTGTT-3' (SEQ ID NO. 31); and

<sup>40</sup> HOB 2gR 5'-CTTCAATCCTGGAGATACCTGG-3' (SEQ ID NO. 32).

4. A detectably labeled nucleic acid molecule of at least 10 nucleotides hybridizable under moderate stringency conditions to a non-coding region of an OB nucleic acid, which non-coding region is selected from the group consisting of

<sup>45</sup> an intron, a 5' non-coding region, and a 3' non-coding region of SEQ ID NOS: 1, 3, 22 or 24.

\* \* \* \* \*

# EXHIBIT 5

6,124,439

167

168

-continued

115

120

125

Arg Leu Gln Gly Ser Leu Gln Asp Met Leu Trp Gln Leu Asp Leu Ser  
130 135 140

Pro Gly Cys  
145

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 21 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

Met Gly Ser Ser His His His His His Ser Ser Gly Leu Val Pro  
1 5 10 15

Arg Gly Ser His Met  
20

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 20 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: N-terminal His-tag

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro  
1 5 10 15

Arg Gly Ser Pro  
20

What is claimed is:

1. An antibody to a mammalian OB polypeptide, said polypeptide having the sequence of a naturally occurring 45 mammalian OB polypeptide, having as a mature protein about 145 amino acids, and capable of modulating body weight.

2. An antibody to an OB polypeptide, the polypeptide comprising:

- a) amino acid sequence set out in SEQ ID NO: 2;
- b) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 2;
- c) the amino acid sequence set out in SEQ ID NO: 4; or
- d) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 4.

3. An antibody to an OB polypeptide, the polypeptide comprising:

- a) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 2 having an N-terminal methionine or an N-terminal polyhistidine; or
- b) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 4 having an N-terminal methionine or an N-terminal polyhistidine.

4. An antibody to an OB polypeptide, the polypeptide comprising:

- a) the amino acid sequence set out in SEQ ID NO: 5;
- b) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 5;
- c) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 5, having an N-terminal methionine or an N-terminal polyhistidine;

d) the amino acid sequence set out in SEQ ID NO: 6;

- e) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 6; or
- f) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 6 having an N-terminal methionine or an N-terminal polyhistidine.

5. An antibody to a variant of an OB polypeptide comprising amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166 is substituted with a conserved amino acid.

6. An antibody to a variant of an OB polypeptide comprising amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166 is substituted with the particular amino acid present at the corresponding position in SEQ ID NO: 2.

7. An antibody to a variant of an OB polypeptide comprising amino acids 22-166 of SEQ ID NO: 6 wherein one or more of amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with a conserved amino acid. 5

8. An antibody to a variant of an OB polypeptide comprising amino acids 22-166 of SEQ ID NO: 6 wherein one or more of amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with the particular amino acid present at the corresponding position in SEQ ID NO: 5. 10

9. An antibody to an immunogenic fragment of an OB polypeptide.

10. An antibody to an immunogenic fragment of an OB polypeptide selected from the group consisting of the polypeptide of SEQ ID NO: 18, the polypeptide of SEQ ID NO: 19, the polypeptide of SEQ ID NO: 20 and the polypeptide of SEQ ID NO: 21. 15

11. An antibody to an OB polypeptide analog wherein the OB polypeptide analog has 83 percent or greater amino acid sequence identity to the OB polypeptide amino acid sequence set out in SEQ ID NOS: 2, 4, 5 or 6.

12. An antibody according to any of claims 1-11 which is a polyclonal, monoclonal, chimeric or single chain antibody. 20

13. An antibody according to any of claims 1-11 which is an Fab, Fab', F(ab')<sub>2</sub> or F(v) portion of a whole antibody molecule.

14. An antibody according to claim 12 which is a humanized monoclonal antibody.

15. An immortal cell line that produces a monoclonal antibody according to claim 12.

16. A method for preparing an antibody specific to an OB polypeptide, comprising: 35

(a) conjugating to a carrier protein a mammalian OB polypeptide, said polypeptide having the sequence of a naturally occurring mammalian OB polypeptide, having as a mature protein about 145 amino acids, and capable of modulating body weight;

(b) immunizing a host animal with the OB polypeptide fragment-carrier protein conjugate of step (a) admixed with an adjuvant; and

(c) obtaining antibody from the immunized host animal.

17. A method for preparing an antibody specific to an OB polypeptide, comprising:

(a) conjugating to a carrier protein an OB polypeptide comprising: 50

i) the amino acid sequence set out in SEQ ID NO: 2; ii) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 2;

iii) the amino acid sequence set out in SEQ ID NO: 4; 55 or

iv) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 4;

(b) immunizing a host animal with the OB polypeptide fragment-carrier protein conjugate of step (a) admixed with an adjuvant; and

(c) obtaining antibody from the immunized host animal.

18. A method for preparing an antibody specific to an OB polypeptide, comprising: 60

(a) conjugating to a carrier protein an OB polypeptide comprising:

i) the amino acid sequence set out in SEQ ID NO: 5; ii) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 5; iii) the amino acid sequence set out in SEQ ID NO: 6; or

iv) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 6;

(b) immunizing a host animal with the OB polypeptide fragment-carrier protein conjugate of step (a) admixed with an adjuvant; and

(c) obtaining antibody from the immunized host animal.

19. A method for preparing an antibody specific to an OB polypeptide, comprising:

(a) conjugating to a carrier protein an immunogenic fragment of an OB polypeptide;

(b) immunizing a host animal with the OB polypeptide fragment-carrier protein conjugate of step (a) admixed with an adjuvant; and

(c) obtaining antibody from the immunized host animal.

20. The method of according to claim wherein the immunogenic fragment is selected from the group of the polypeptide of SEQ ID NO: 18, the polypeptide of SEQ ID NO: 19,

25 the polypeptide of SEQ ID NO: 20, and the polypeptide of SEQ ID NO: 21.

21. A method for preparing an antibody specific to an OB polypeptide, comprising:

(a) conjugating to a carrier protein an OB polypeptide comprising amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166 is substituted with a conserved amino acid;

(b) immunizing a host animal with the OB polypeptide fragment-carrier protein conjugate of step (a) admixed with an adjuvant; and

(c) obtaining antibody from the immunized host animal.

22. A method for preparing an antibody specific to an OB polypeptide, comprising:

(a) conjugating to a carrier protein an OB polypeptide comprising amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166 is substituted with the particular amino acid present at the corresponding position in SEQ ID NO: 2;

(b) immunizing a host animal with the OB polypeptide fragment-carrier protein conjugate of step (a) admixed with an adjuvant; and

(c) obtaining antibody from the immunized host animal.

23. A method for preparing an antibody specific to an OB polypeptide, comprising:

(a) conjugating to a carrier protein an OB polypeptide having 83 percent or greater amino acid sequence identity to the OB polypeptide amino acid sequence set out in SEQ ID NOS: 2, 4, 5 or 6;

(b) immunizing a host animal with the OB polypeptide fragment-carrier protein conjugate of step (a) admixed with an adjuvant; and

(c) obtaining antibody from the immunized host animal.

24. A test kit for determining the presence or amount of OB polypeptide comprising:

- (a) a predetermined amount of at least one labeled antibody to an OB polypeptide obtained by the direct or indirect attachment of an antibody to an OB polypeptide to a detectable label;
- (b) other reagents; and
- (c) directions for use of said kit.

25. A test kit for determining the presence or amount of OB polypeptide comprising:

- (a) a labeled component which has been obtained by coupling an OB polypeptide to a detectable label;

(b) one or more additional immunochemically reactive components of which at least one component is an antibody to an OB polypeptide; and

- (c) directions for the performance of a protocol for the detection and/or determination of one or more components of an immunochemical reaction between OB polypeptide and an antibody to an OB polypeptide.

26. A test kit of claim 24 or 25, wherein the kit determines the presence or amount of OB polypeptide in an individual's blood or plasma.

27. A test kit of claim 24 or 25, wherein the detectable label is radioactive, enzymatic, fluorescent or calorimetric.

\* \* \* \* \*

## (2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 20 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: N-terminal His-tag

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

Met Gly Ser Ser His His His His His Ser Ser Gly Leu Val Pro  
 1 5 10 15  
 Arg Gly Ser Pro  
 20

What is claimed is:

1. A method for modifying body weight of an animal comprising administering an effective amount of a mammalian OB polypeptide, said polypeptide having the sequence of a naturally occurring mammalian OB polypeptide, having as a mature protein about 145 amino acids, and capable of modulating body weight.

2. A method for modifying body weight of an animal comprising administering an effective amount of an OB polypeptide capable of modulating body weight, the polypeptide comprising:

- a) the amino acid sequence set out in SEQ ID NO: 2;
- b) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 2;
- c) the amino acid sequence set out in SEQ ID NO: 4; or
- d) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 4.

3. A method for modifying body weight of an animal comprising administering an effective amount of an OB polypeptide capable of modulating body weight, the polypeptide comprising:

- a) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 2 having an N-terminal methionine or an N-terminal polyhistidine; or
- b) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 4 having an N-terminal methionine or an N-terminal polyhistidine.

4. A method for modifying body weight of an animal comprising administering an effective amount of an OB polypeptide capable of modulating body weight, the polypeptide comprising:

- a) the amino acid sequence set out in SEQ ID NO: 5;
- b) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 5;
- c) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 5, having an N-terminal methionine or an N-terminal polyhistidine;
- d) the amino acid sequence set out in SEQ ID NO: 6;
- e) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 6; or
- f) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO: 6 having an N-terminal methionine or an N-terminal polyhistidine.

5. A method for modifying body weight of an animal comprising administering an effective amount of a variant of

an OB polypeptide, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166 is substituted with:

- a) the amino acid present in SEQ ID NO:3 at the corresponding position; or
- b) a conserved amino acid.

6. A method for modifying body weight of an animal comprising administering an effective amount of a variant of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NO:4, wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 121, 122, 126, 127, 128, 129, 139, 157, 159 and 163 is substituted with the particular amino acid present at the corresponding position in SEQ ID NO: 2.

7. A method for modifying body weight of an animal comprising administering an effective amount of a variant of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NO: 6 wherein one or more of amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with:

- a) the amino acid present in SEQ ID NO: 5 at the corresponding position; or
- b) a conserved amino acid.

8. A method for modifying body weight of an animal comprising administering an effective amount of a variant of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NO: 6 wherein one or more of amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 120, 121, 125, 126, 127, 128, 138, 156, 158 and 162 is substituted with the particular amino acid present at the corresponding position in SEQ ID NO: 5.

9. The method according to claim 2 wherein said OB polypeptide comprises amino acids 22-167 of SEQ ID NO: 4, optionally having an N-terminal methionine, in a pharmaceutically acceptable carrier.

10. The method according to any of claims 1-9 wherein said OB polypeptide is a recombinant OB polypeptide.

11. The method according to any of claims 1-9 wherein said OB polypeptide is a chemically synthesized OB polypeptide.

\* \* \* \* \*

-continued

Leu Glu Asn Leu Arg Asp Leu Leu His Val Leu Ala Phe Ser Lys Ser  
 85 90 95

Cys His Leu Pro Trp Ala Ser Gly Leu Glu Thr Leu Asp Ser Leu Gly  
 100 105 110

Gly Val Leu Glu Ala Ser Gly Tyr Ser Thr Glu Val Val Ala Leu Ser  
 115 120 125

Arg Leu Gln Gly Ser Leu Gln Asp Met Leu Trp Gln Leu Asp Leu Ser  
 130 135 140

Pro Gly Cys  
 145

## (2) INFORMATION FOR SEQ ID NO: 98:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 21 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

Met Gly Ser Ser His His His His Ser Ser Gly Leu Val Pro  
 1 5 10 15

Arg Gly Ser His Met  
 20

What is claimed is:

1. A method for modifying body weight of an animal, the method comprising administering to the animal an effective amount of an OB polypeptide analog, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NOS: 2 or 4, wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163, and 166 is substituted with another amino acid.

2. A method for modifying body weight of an animal, the method comprising administering to the animal an effective amount of an OB polypeptide analog, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NO: 4 wherein the analog is selected from the group consisting of polypeptides wherein:

(a) the serine residue at position 53 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine;

(b) the serine residue at position 98 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine; and

(c) the arginine residue at position number 92 is substituted with asparagine, lysine, histidine, glutamine, glutamic acid, aspartic acid, serine, threonine, methionine, or cysteine.

3. A method for modifying body weight of an animal, the method comprising administering to the animal an effective amount of an OB polypeptide, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NOS: 2 or 4 or amino acids 22-166 of SEQ ID NO: 5 or 6 wherein said polypeptide has an N-terminal amino acid sequence selected from the group consisting of:

- (a) SEQ ID NO: 38;
- (b) SEQ ID NO: 98;
- (c) SEQ ID NO: 26;
- (d) SEQ ID NO: 27;
- (e) SEQ ID NO: 28;
- (f) SEQ ID NO: 99; and
- (g) glycine-serine-proline.

4. A method for modifying body weight of an animal, the method comprising administering to the animal an effective amount of an OB polypeptide analog, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NOS: 2 or 4, wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163, and 166 is substituted with another amino acid and wherein said analog has an N-terminal amino acid sequence selected from the group consisting of:

- (a) SEQ ID NO: 38;
- (b) SEQ ID NO: 98;
- (c) SEQ ID NO: 26;
- (d) SEQ ID NO: 27;
- (e) SEQ ID NO: 28;
- (f) SEQ ID NO: 99; and
- (g) glycine-serine-proline.

5. A method for modifying body weight of an animal, the method comprising administering to the animal an effective amount of an OB polypeptide analog, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NOS: 5 or 6, wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162, and 165 is substituted with another amino acid.

6. A method for modifying body weight of an animal, the method comprising administering to the animal an effective amount of an OB polypeptide analog, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NO: 6 wherein the analog is selected from the group consisting of polypeptides wherein:

- (a) the serine residue at position 52 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine;
- (b) the serine residue at position 97 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine; and
- (c) the arginine residue at position number 91 is substituted with asparagine, lysine, histidine, glutamine, glutamic acid, aspartic acid, serine, threonine, methionine, or cysteine.

7. A method for modifying body weight of an animal, the method comprising administering to the animal an effective amount of an OB polypeptide analog, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NOS: 5 or 6, wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162, and 165 is substituted with another amino acid and wherein said analog has an N-terminal amino acid sequence selected from the group consisting of:

- (a) SEQ ID NO: 38;
- (b) SEQ ID NO: 98;
- (c) SEQ ID NO: 26;
- (d) SEQ ID NO: 27;
- (e) SEQ ID NO: 28;
- (f) SEQ ID NO: 99; and
- (g) glycine-serine-proline.

8. The method according to claim 1, 2, 3, 4, 5, 6, or 7 wherein the OB polypeptide or polypeptide analog is a recombinant polypeptide or polypeptide analog.

9. The method according to claim 1, 2, 3, 4, 5, 6, or 7 wherein the OB polypeptide or polypeptide analog is a chemically synthesized polypeptide or polypeptide analog.

10. The method according to claim 1, 2, 3, 4, 5, 6, or 7 wherein the OB polypeptide or polypeptide analog has one or more polymers attached thereto.

11. The method according to claim 10, wherein at least one of said polymers is a water-soluble polymer.

12. The method according to claim 11, wherein the water-soluble polymer is polyethylene glycol.

13. The method according to claim 12, wherein the polypeptide or polypeptide analog is mono-, di-, tri- or tetrapegylated.

14. The method according to claim 13 wherein the polypeptide or polypeptide analog is N-terminal monopegylated.

15. The method according to claim 10, wherein at least one of said polymers is a pharmaceutically acceptable polymer.

16. The method according to claim 15, wherein said pharmaceutically acceptable polymer is a water soluble polymer.

17. The method according to claim 10, wherein at least one of said polymers is a polyamino acid.

18. The method according to claim 10, wherein at least one of said polymers is a branched or unbranched polymer.

19. The method according to claim 10, wherein at least one of said polymers is N-terminally attached to said polypeptide or polypeptide analog.

20. The method according to claim 10, wherein at least one of said polymers is C-terminally attached to said polypeptide or polypeptide analog.

21. The method according to claim 10, wherein at least one of said polymers is attached by at least one covalent bond through an amino acid residue of said polypeptide or polypeptide analog via a reactive group.

22. The method according to claim 21, wherein said reactive group is a free amino or carboxyl group.

23. The method according to claim 21, wherein said amino acid residue is selected from the group consisting of lysine, aspartic acid and glutamic acid.

24. The method according to claim 10, wherein the number of said polymers attached is one, two, three or four.

25. The method according to claim 24 wherein said two, three or four polymers are the same polymer.

26. The method according to claim 24 wherein said two, three or four polymers are two, three or four different polymers.

27. The method according to claim 1, 2, 3, 4, 5, 6 or 7 wherein the OB polypeptide or polypeptide analog is administered by intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, nasal, oral or pulmonary delivery.

\* \* \* \* \*

## PRESENTLY PENDING CLAIMS

124. (Three Times Amended) A method for modifying the body weight of a mammal comprising administering to the mammal a vector comprising a nucleic acid molecule encoding an OB polypeptide under conditions that provide for expression of the OB polypeptide *in vivo*, such OB polypeptide capable of modulating body weight and selected from the group consisting of:

- a) the amino acid sequence set out in SEQ ID NO: 2;
- b) the amino acid sequence set out in amino acids 22-167 of SEQ. ID.

NO: 2;

- c) the amino acid sequence set out in amino acids 22-167 of SEQ. ID.

NO: 2, having an N-terminal methionine or an N-terminal polyhistidine;

- d) the amino acid sequence set out in SEQ ID NO: 4;
- e) the amino acid sequence set out in amino acids 22-167 of SEQ. ID.

NO: 4; and

- f) the amino acid sequence set out in amino acids 22-167 of SEQ. ID.

NO: 4, having an N-terminal methionine or an N-terminal polyhistidine.

132. (Twice Amended) A method for modifying the body weight of a mammal comprising administering to the mammal a vector comprising a nucleic acid molecule encoding a OB polypeptide under conditions that provide for expression of the OB polypeptide *in vivo*, such OB polypeptide capable of modulating body weight and selected from the group consisting of:

- a) the amino acid sequence set out in SEQ ID NO: 5;
- b) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO:

5;

- c) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO:

5, having an N-terminal methionine or an N-terminal polyhistidine;

- d) the amino acid sequence set out in SEQ ID NO: 6;
- e) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO:

6; and

- f) the amino acid sequence set out in amino acids 22-166 of SEQ ID NO:

6, having an N-terminal methionine or an N-terminal polyhistidine.

133. (Twice Amended) A method for modifying the body weight of a mammal comprising administering to the mammal a vector comprising a nucleic acid molecule encoding an OB polypeptide under conditions that provide for expression of the OB polypeptide *in vivo*, such OB polypeptide capable of modulating body weight wherein such OB polypeptide has 83 percent or more amino acid identity to the OB polypeptide amino acid sequence set out in SEQ ID NOS: 2, 4, 5, 6, 23 or 25.

134. (Twice Amended) A method for modifying the body weight of a mammal comprising administering to the mammal a vector comprising a nucleic acid molecule encoding an analog of an OB polypeptide under conditions that provide for expression of the OB polypeptide analog *in vivo*, such OB polypeptide analog capable of modulating body weight and comprising amino acids 22-167 of SEQ ID NO:4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166 is substituted with another amino acid.

135. (Twice Amended) A method for modifying the body weight of a mammal comprising administering to the mammal a vector comprising a nucleic acid molecule encoding an analog of an OB polypeptide under conditions that provide for expression of the OB polypeptide analog *in vivo*, such OB polypeptide analog capable of modulating body weight and comprising amino acids 22-166 of SEQ ID NO:6 wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with another amino acid.

136. (Amended) A method according to claim 163 wherein said mammal is a mouse.

137. (Amended) A method according to claim 163 wherein said mammal is a human.

139. (Twice Amended) A method of delivering DNA encoding an OB polypeptide

capable of modulating body weight to a mammal comprising administering to said mammal a vector which comprises such OB encoding DNA operatively associated with an expression control sequence, under conditions that provide for the expression of the OB polypeptide by the mammal wherein said OB polypeptide is selected from the group consisting of:

- a) the amino acid sequence set out in SEQ ID NO: 2;
- b) the amino acid sequence set out in amino acids 22-167 of SEQ. ID.

NO: 2;

- c) the amino acid sequence set out in amino acids 22-167 of SEQ. ID.

NO: 2, having an N-terminal methionine or an N-terminal polyhistidine;

- d) the amino acid sequence set out in SEQ ID NO: 4;
- e) the amino acid sequence set out in amino acids 22-167 of SEQ. ID.

NO: 4; and

- f) the amino acid sequence set out in amino acids 22-167 of SEQ. ID.

NO: 4, having an N-terminal methionine or an N-terminal polyhistidine.

140. (Twice Amended) A method of delivering DNA encoding an OB polypeptide capable of modulating body weight to a mammal comprising administering to said mammal a vector which comprises such OB encoding DNA operatively associated with an expression control sequence, under conditions that provide for the expression of the OB polypeptide by the mammal wherein said OB polypeptide is selected from the group consisting of the amino acid sequence set forth in:

- a) SEQ ID NO: 5;
- b) amino acids 22-166 of SEQ ID NO: 5;
- c) amino acids 22-166 of SEQ ID NO: 5, having an N-terminal methionine

or an N-terminal polyhistidine;

- d) SEQ ID NO: 6;
- e) amino acids 22-166 of SEQ ID NO: 6; and
- f) amino acids 22-166 of SEQ ID NO: 6, having an N-terminal methionine

or an N-terminal polyhistidine.

141. (Twice Amended) A method of delivering DNA encoding an OB polypeptide capable of modulating body weight to a mammal comprising administering to said mammal a vector which comprises such OB encoding DNA operatively associated with an expression

control sequence, under conditions that provide for expression of the OB polypeptide by the mammal, wherein said OB polypeptide has 83 percent or greater amino acid identity to the OB polypeptide amino acid sequence set out in SEQ ID NOS: 2, 4, 5, 6, 23 or 25.

142. (Twice Amended) A method of delivering DNA encoding an analog of an OB polypeptide capable of modulating body weight to a mammal comprising administering to said mammal a vector which comprises such OB encoding DNA operatively associated with an expression control sequence, under conditions that provide for expression of the OB polypeptide analog by the mammal. said OB polypeptide analog comprising amino acids 22-167 of SEQ ID NO:4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166 is substituted with another amino acid.

143. (Twice Amended) A method of delivering DNA encoding an analog of an OB polypeptide capable of modulating body weight to a mammal comprising administering to said mammal a vector which comprises such OB encoding DNA operatively associated with an expression control sequence, under conditions that provide for expression of the OB polypeptide analog by the mammal, said OB polypeptide analog comprising amino acids 22-166 of SEQ ID NO:6 wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with another amino acid.

145. (Twice Amended) A method of expressing an OB polypeptide in a mammal comprising administering to said mammal a DNA vector which vector comprises DNA encoding an OB polypeptide capable of modulating body weight operatively associated with an expression control sequence wherein said OB polypeptide is selected from the group consisting of:

- a) the amino acid sequence set out in SEQ ID NO: 2;
- b) the amino acid sequence set out in amino acids 22-167 of SEQ. ID. NO: 2;
- c) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 2, having an N-terminal methionine or an N-terminal polyhistidine;
- d) the amino acid sequence set out in SEQ ID NO: 4;
- e) the amino acid sequence set out in amino acids 22-167 of SEQ. ID.

NO: 4; and

- f) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO: 4, having an N-terminal methionine or an N-terminal polyhistidine.

146. (Twice Amended) A method of expressing an OB polypeptide in a mammal comprising administering to said mammal a DNA vector which vector comprises DNA encoding an OB polypeptide capable of modulating body weight operatively associated with an expression control sequence wherein said OB polypeptide is selected from the group consisting of the amino acid sequence set forth in:

- a) SEQ ID NO: 5;
- b) amino acids 22-166 of SEQ ID NO: 5;
- c) amino acids 22-166 of SEQ ID NO: 5, having an N-terminal methionine or an N-terminal polyhistidine;
- d) SEQ ID NO: 6;
- e) amino acids 22-166 of SEQ ID NO: 6; and
- f) amino acids 22-166 of SEQ ID NO: 6, having an N-terminal methionine or an N-terminal polyhistidine.

147. (Twice Amended) A method of expressing an OB polypeptide in a mammal comprising administering to said mammal a DNA vector which vector comprises DNA encoding an OB polypeptide capable of modulating body weight operatively associated with an expression control sequence wherein said OB polypeptide has 83 percent or greater amino acid identity to the OB polypeptide amino acid sequence set out in SEQ ID NOS: 2, 4, 5, 6, 23 or 25.

148. (Twice Amended) A method of expressing an analog of an OB polypeptide in a mammal comprising administering to said mammal a DNA vector which vector comprises DNA encoding an OB polypeptide analog capable of modulating body weight operatively associated with an expression control sequence, said OB polypeptide analog comprising amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166 is substituted with another amino acid.

149. (Twice Amended) A method of expressing an analog of an OB polypeptide in a mammal comprising administering to said mammal a DNA vector which vector comprises DNA encoding an OB polypeptide analog capable of modulating body weight operatively associated with an expression control sequence, said OB polypeptide analog comprising amino acids 22-166 of SEQ ID NO:6 wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with another amino acid.

155. (Twice Amended) A method of expressing an OB polypeptide in a mammal comprising administering to said mammal a mammalian cell comprising an expression vector which vector comprises DNA encoding an OB polypeptide capable of modulating body weight operatively associated with an expression control sequence under conditions that provide for expression of the OB polypeptide by the mammal wherein said OB polypeptide is selected from the group consisting of:

- a) the amino acid sequence set out in SEQ ID NO: 2;
- b) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO:

NO: 2;

- c) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO:

2, having an N-terminal methionine or an N-terminal polyhistidine;

- d) the amino acid sequence set out in SEQ ID NO: 4;

- e) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO:

NO: 4;

and

- f) the amino acid sequence set out in amino acids 22-167 of SEQ ID NO:

4, having an N-terminal methionine or an N-terminal polyhistidine.

156. (Twice Amended) A method of expressing an OB polypeptide in a mammal comprising administering to said mammal a mammalian cell comprising an expression vector which vector comprises DNA encoding an OB polypeptide capable of modulating body weight operatively associated with an expression control sequence under conditions that provide for expression of the OB polypeptide by the mammal wherein said OB polypeptide is selected from the group consisting of the amino acid sequence set forth in:

- a) SEQ ID NO: 5;
- b) amino acids 22-166 of SEQ ID NO: 5;

- c) amino acids 22-166 of SEQ ID NO: 5, having an N-terminal methionine or an N-terminal polyhistidine;
- d) SEQ ID NO: 6;
- e) amino acids 22-166 of SEQ ID NO: 6; and
- f) amino acids 22-166 of SEQ ID NO: 6, having an N-terminal methionine or an N-terminal polyhistidine.

157. (Twice Amended) A method of expressing an OB polypeptide in a mammal comprising administering to said mammal a mammalian cell comprising an expression vector which vector comprises DNA encoding an OB polypeptide capable of modulating body weight operatively associated with an expression control sequence under conditions that provide for expression of the OB polypeptide by the mammal wherein said OB polypeptide has 83 percent or greater amino acid identity to the OB polypeptide amino acid sequence set out in SEQ ID NOS: 2, 4, 5, 6, 23 or 25.

158. (Twice Amended) A method of expressing an analog of an OB polypeptide in a mammal comprising administering to said mammal a mammalian cell comprising an expression vector which vector comprises DNA encoding an OB polypeptide analog capable of modulating body weight operatively associated with an expression control sequence, under conditions that provide for expression of the OB polypeptide analog by the mammal, said OB polypeptide analog comprising amino acids 22-167 of SEQ ID NO:4 wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166 is substituted with another amino acid.

159. (Twice Amended) A method of expressing an analog of an OB polypeptide in a mammal comprising administering to said mammal a mammalian cell comprising an expression vector which vector comprises DNA encoding an OB polypeptide analog capable of modulating body weight operatively associated with an expression control sequence, under conditions that provide for expression of the OB polypeptide analog by the mammal, said OB polypeptide analog comprising amino acids 22-166 of SEQ ID NO:6 wherein one or more of amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with another amino acid.

165. A method for modifying the body weight of a mammal comprising administering to the mammal a vector comprising a nucleic acid molecule encoding an OB polypeptide analog under conditions that provide for expression of the polypeptide analog *in vivo*, said analog, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NOS: 2 or 4 wherein said analog is selected from the group consisting of polypeptides wherein:

- (a) the serine residue at position 53 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine;
- (b) the serine residue at position 98 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine; and
- (c) the arginine residue at position number 92 is substituted with asparagine, lysine, histidine, glutamine, glutamic acid, aspartic acid, serine, threonine, methionine, or cysteine.

166. A method for modifying the body weight of a mammal comprising administering to the mammal a vector comprising a nucleic acid molecule encoding an OB polypeptide analog under conditions that provide for expression of the polypeptide analog *in vivo*, said analog, capable of modulating body weight, comprising an amino acid sequence of SEQ ID NOS: 2 or 4, wherein said analog is selected from the group consisting of polypeptides wherein:

- (a) one or more aspartic acid residues is substituted with glutamic acid;
- (b) one or more isoleucine residues is substituted with leucine;
- (c) one or more glycine or valine residues is substituted with alanine;
- (d) one or more arginine residues is substituted with histidine;
- (e) one or more tyrosine or phenylalanine residues is substituted with tryptophan;
- (f) one or more of residues 121 through 128 is substituted with glycine or alanine; and
- (g) one or more residues at positions 54 through 60 or 118 through 166 is substituted with lysine, glutamic acid, cysteine, or proline.

167. A method for modifying the body weight of a mammal comprising administering to the mammal a vector comprising a nucleic acid molecule encoding an OB polypeptide under conditions that provide for expression of the polypeptide *in vivo*, said

polypeptide, capable of modulating body weight, comprising the amino acid sequences set out in amino acids 22-167 of SEQ ID NOS: 2 or 4 or in amino acids 22-166 of SEQ ID NOS: 5 or 6 wherein said polypeptide has an N-terminal amino acid sequence selected from the group consisting of:

- (a) SEQ ID NO: 38;
- (b) SEQ ID NO: 98;
- (a) SEQ ID NO: 26;
- (b) SEQ ID NO: 27;
- (c) SEQ ID NO: 28;
- (d) SEQ ID NO: 99; and
- (e) glycine-serine-proline.

168. A method for modifying the body weight of a mammal comprising administering to the mammal a vector comprising a nucleic acid molecule encoding an OB polypeptide analog under conditions that provide for expression of the polypeptide analog *in vivo*, said analog, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NOS: 2 or 4, wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163, and 166 is substituted with another amino acid and wherein said analog has an N-terminal amino acid or amino acid sequence selected from the group consisting of:

- (a) methionine;
- (b) SEQ ID NO: 38;
- (c) SEQ ID NO: 98;
- (d) SEQ ID NO: 26;
- (e) SEQ ID NO: 27;
- (f) SEQ ID NO: 28;
- (g) SEQ ID NO: 99; and
- (h) glycine-serine-proline.

169. A method for modifying the body weight of a mammal comprising administering to the mammal a vector comprising a nucleic acid molecule encoding an OB polypeptide analog under conditions that provide for expression of the polypeptide analog *in vivo*, said analog, capable of modulating body weight, comprising an amino acid sequence of SEQ ID NOS: 2 or 4, wherein said analog is a truncated analog selected from the group

consisting of polypeptides wherein:

- (a) one or more residues at positions 121 to 128 are deleted;
- (b) residues 1-116 are deleted;
- (c) residues 1-21 and 54 to 167 are deleted;
- (d) residues 1-60 and 117 to 167 are deleted;
- (e) residues 1-60 are deleted;
- (f) residues 1-53 are deleted;
- (g) an analog of subpart (a) wherein residues 1-21 are deleted; and
- (h) an analog of any of subparts (a) through (g) having an N-terminal

amino acid or amino acid sequence selected from the group consisting of:

- (1) methionine,
- (2) SEQ ID NO: 38,
- (3) SEQ ID NO: 98,
- (4) SEQ ID NO: 26,
- (5) SEQ ID NO: 27,
- (6) SEQ ID NO: 28,
- (7) SEQ ID NO: 99, and
- (8) glycine-serine-proline.

170. A method for modifying the body weight of a mammal comprising administering to the mammal a vector comprising a nucleic acid molecule encoding an OB polypeptide analog under conditions that provide for expression of the polypeptide analog *in vivo*, said analog, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NOS: 5 or 6 wherein said analog is selected from the group consisting of polypeptides wherein:

- (a) the serine residue at position 52 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine;
- (b) the serine residue at position 97 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine; and
- (c) the arginine residue at position number 91 is substituted with asparagine, lysine, histidine, glutamine, glutamic acid, aspartic acid, serine, threonine, methionine, or cysteine.

171. A method for modifying the body weight of a mammal comprising

administering to the mammal a vector comprising a nucleic acid molecule encoding an OB polypeptide analog under conditions that provide for expression of the polypeptide analog *in vivo*, said analog, capable of modulating body weight, comprising an amino acid sequence of SEQ ID NOS: 5 or 6, wherein said analog is selected from the group consisting of polypeptides wherein:

- (a) one or more aspartic acid residues is substituted with glutamic acid;
- (b) one or more isoleucine residues is substituted with leucine;
- (c) one or more glycine or valine residues is substituted with alanine;
- (d) one or more arginine residues is substituted with histidine;
- (e) one or more tyrosine or phenylalanine residues is substituted with tryptophan;
- (f) one or more of residues 120 through 127 is substituted with glycine or alanine; and
- (g) one or more residues at positions 53 through 59 or 117 through 165 is substituted with lysine, glutamic acid, cysteine, or proline.

172. A method for modifying the body weight of a mammal comprising administering to the mammal a vector comprising a nucleic acid molecule encoding an OB polypeptide analog under conditions that provide for expression of the polypeptide analog *in vivo*, said analog, capable of modulating body weight, comprising an amino acid sequence of SEQ ID NOS: 5 or 6, wherein said analog is a truncated analog selected from the group consisting of polypeptides wherein:

- (a) one or more residues at positions 120 through 127 are deleted;
- (b) residues 1-115 are deleted;
- (c) residues 1-21 and 53 to 166 are deleted;
- (d) residues 1-59 and 116 to 166 are deleted;
- (e) residues 1-59 are deleted;
- (f) residues 1-52 are deleted;
- (g) an analog of subpart (a) wherein residues 1-21 are deleted; and
- (h) an analog of any of subparts (a) through (g) having an N-terminal amino acid or amino acid sequence selected from the group consisting of:

- (1) methionine,
- (2) SEQ ID NO: 38,

- (3) SEQ ID NO: 98,
- (4) SEQ ID NO: 26,
- (5) SEQ ID NO: 27,
- (6) SEQ ID NO: 28,
- (7) SEQ ID NO: 99, and
- (8) glycine-serine-proline.

173. A method for modifying the body weight of a mammal comprising administering to the mammal a vector comprising a nucleic acid molecule encoding an OB polypeptide analog under conditions that provide for expression of the polypeptide analog *in vivo*, said analog, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NOS: 5 or 6, wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162, and 165 is substituted with another amino acid and wherein said analog has an N-terminal amino acid or amino acid sequence selected from the group consisting of:

- (a) methionine;
- (b) SEQ ID NO: 38;
- (c) SEQ ID NO: 98;
- (d) SEQ ID NO: 26;
- (e) SEQ ID NO: 27;
- (f) SEQ ID NO: 28;
- (g) SEQ ID NO: 99; and
- (h) glycine-serine-proline.

# EXHIBIT N

## CLAIMS PENDING UPON ENTRY OF INSTANT AMENDMENT

54. A method of treating obesity in a mammal having a deficiency in functional leptin comprising administering intravenously to the mammal an adenoviral vector comprising a DNA sequence encoding a leptin operably linked to a promoter and expressing the DNA sequence, wherein the mammal exhibits a decrease in body weight, a decrease in serum glucose levels and/or a decrease in serum insulin levels.

55. A method according to claim 54 wherein the adenoviral vector is expressed in liver.

56. A method according to claim 54 wherein the mammal is a human.

57. [Amended] A method for treating obesity in a mammal comprising administering to the mammal an adenoviral vector comprising a DNA sequence encoding an OB polypeptide operably linked to an expression control sequence and expressing the DNA sequence wherein the mammal exhibits a decrease in body weight, a decrease in glucose levels and/or decrease in insulin levels.

58. The method according to claim 57 wherein the mammal has a deficiency in functional leptin.

59. The method according to claim 57 or 58 wherein the adenoviral vector is administered intravenously to the mammal.

62. The method of claim 57 or 58 wherein the mammal is a human.

63. The method of claim 59 wherein the mammal is human.

-continued

Met	Gly	Ser	Ser	His	His	His	His	Ser	Ser	Gly	Leu	Val	Pro
1				5			10			15			
Arg	Gly	Ser	His	Met									20

What is claimed is:

1. An immunogenic fragment of an OB polypeptide, said fragment selected from the group consisting of:
  - (a) SEQ ID NO: 18;
  - (b) SEQ ID NO: 19;
  - (c) SEQ ID NO: 20; and
  - (d) SEQ ID NO: 21.
2. An OB polypeptide analog, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NOS: 2 or 4, wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163, and 166 is substituted with another amino acid.
3. An OB polypeptide analog, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NO: 4 wherein the analog is selected from the group consisting of polypeptides wherein:
  - (a) the serine residue at position 53 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine;
  - (b) the serine residue at position 98 is substituted with glycine, alanine, saline, cysteine, methionine, or threonine; and
  - (c) the arginine residue at position number 92 is substituted with asparagine, lysine, histidine, glutamine, glutamic acid, aspartic acid, serine, threonine, methionine, or cysteine.
4. An OB polypeptide capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NOS: 2 or 4 or amino acids 22-166 of SEQ ID NO: 5 or 6, wherein said polypeptide has an N-terminal amino acid sequence selected from the group consisting of:
  - (a) SEQ ID NO: 38;
  - (b) SEQ ID NO: 98;
  - (c) SEQ ID NO: 26;
  - (d) SEQ ID NO: 27;
  - (e) SEQ ID NO: 28;
  - (f) SEQ ID NO: 99; and
  - (g) glycine-serine-proline.
5. An OB polypeptide analog, capable of modulating body weight, comprising amino acids 22-167 of SEQ ID NOS: 2 or 4, wherein one or more amino acids selected from the group consisting of amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163, and 166 is substituted with another amino acid and wherein said analog has an N-terminal amino acid sequence selected from the group consisting of:
  - (a) SEQ ID NO: 38;
  - (b) SEQ ID NO: 98;
  - (c) SEQ ID NO: 26;
  - (d) SEQ ID NO: 27;
  - (e) SEQ ID NO: 28;
  - (f) SEQ ID NO: 99; and
  - (g) glycine-serine-proline.
6. An OB polypeptide analog, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NOS: 5 or 6, wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162, and 165 is substituted with another amino acid.
7. An OB polypeptide analog, capable of modulating body weight, comprising amino acids 22-166 of SEQ ID NO: 6 wherein the analog is selected from the group consisting of polypeptides wherein:
  - (a) the serine residue at position 52 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine;
  - (b) the serine residue at position 97 is substituted with glycine, alanine, valine, cysteine, methionine, or threonine; and
  - (c) the arginine residue at position number 91 is substituted with asparagine, lysine, histidine, glutamine, glutamic acid, aspartic acid, serine, threonine, methionine, or cysteine.
8. An OB polypeptide analog, capable of modulating body weight, comprising an amino acids 22-166 of SEQ ID NOS: 5 or 6, wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162, and 165 is substituted with another amino acid and wherein said analog has an N-terminal amino acid sequence selected from the group consisting of:
  - (a) SEQ ID NO: 38;
  - (b) SEQ ID NO: 98;
  - (c) SEQ ID NO: 26;
  - (d) SEQ ID NO: 27;
  - (e) SEQ ID NO: 28;
  - (f) SEQ ID NO: 99; and
  - (g) glycine-serine-proline.
9. A recombinant OB polypeptide or polypeptide analog according to any of claims 2, 3, 4, 5, 6, 7, or 8.
10. A chemically synthesized OB polypeptide or polypeptide analog according to any of claims 2, 3, 4, 5, 6, 7, or 8.
11. An OB polypeptide or polypeptide analog according to any of claims 2, 3, 4, 5, 6, 7, or 8 having one or more polymers attached thereto.
12. The polypeptide or analog of claim 11, wherein at least one of said polymers is a water soluble polymer.
13. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 12 and a pharmaceutically acceptable carrier.
14. The polypeptide or analog of claim 12, wherein the water soluble polymer is polyethylene glycol.
15. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 14 and a pharmaceutically acceptable carrier.
16. The polypeptide or analog of claim 14, which is mono-, di-, tri- or tetrapegylated.
17. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 16 and a pharmaceutically acceptable carrier.

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18. The polypeptide or analog of claim 16, which is N-terminal monopegylated.

19. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 18 and a pharmaceutically acceptable carrier.

20. The polypeptide or analog of claim 11, wherein at least one of said polymers is a pharmaceutically acceptable polymer.

21. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 20 and a pharmaceutically acceptable carrier.

22. The polypeptide or analog of claim 20, wherein said pharmaceutically acceptable polymer is a water soluble polymer.

23. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 22 and a pharmaceutically acceptable carrier.

24. The polypeptide or analog of claim 11, wherein at least one of said polymers is a polyamino acid.

25. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 24 and a pharmaceutically acceptable carrier.

26. The polypeptide or analog of claim 11, wherein at least one of said polymers is a branched or unbranched polymer.

27. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 26 and a pharmaceutically acceptable carrier.

28. The polypeptide or analog of claim 11, wherein at least one of said polymers is N-terminally attached to said polypeptide or polypeptide analog.

29. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 28 and a pharmaceutically acceptable carrier.

30. The polypeptide or analog of claim 11, wherein at least one of said polymers is C-terminally attached to said polypeptide or polypeptide analog.

31. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 30 and a pharmaceutically acceptable carrier.

32. The polypeptide or analog of claim 11, wherein at least one of said polymers is attached by at least one

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covalent bond through an amino acid residue of said polypeptide or polypeptide analog via a reactive group.

33. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 32 and a pharmaceutically acceptable carrier.

34. The polypeptide or analog of claim 32, wherein said reactive group is a free amino or carboxyl group.

35. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 34 and a pharmaceutically acceptable carrier.

36. The polypeptide or analog of claim 32, wherein said amino acid residue is selected from the group consisting of lysine, aspartic acid and glutamic acid.

37. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 36 and a pharmaceutically acceptable carrier.

38. The polypeptide or analog of claim 11, wherein the number of said polymers attached is one, two, three or four.

39. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 38 and a pharmaceutically acceptable carrier.

40. The polypeptide or analog of claim 38 wherein said two, three or four polymers are the same polymer.

41. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 40 and a pharmaceutically acceptable carrier.

42. The polypeptide or analog of claim 38 wherein said two, three or four polymers are two, three or four different polymers.

43. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 42 and a pharmaceutically acceptable carrier.

44. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to claim 11 and a pharmaceutically acceptable carrier.

45. A pharmaceutical composition comprising an OB polypeptide or polypeptide analog according to any of claims 2, 3, 4, 5, 6, 7, or 8 and a pharmaceutically acceptable carrier.

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